I. PETITION FOR EXTENSION OF TIME

A request for a three-month extension of time to respond is included herewith along with the required extension fee ($460.00). This 3-month extension will bring the due date to September 18, 2002, which is within the six-month statutory period. Should such request or fee be deficient or absent, consider this paragraph such a request and authorization to withdraw the appropriate fee under 37 C.F.R. §§ 1.16 to 1.21 from Fulbright & Jaworski L.L.P. Account No.: 50-1212/10016657/01982.

II. AMENDMENTS

Please make the following amendments:

In the Claims:

Please add new claims 100, 101, 102, 103 104, 105, 106, 107, and 108 as set forth below and amend claims 26, 84, 85, 86, 87, 88, 89, 90, 91, 93, 94, 95, 96, 97, 98 and 99 as follows:

26.(amended) A pharmaceutically acceptable solvent vehicle prepared by a process comprising;

a) obtaining a pharmaceutically acceptable dipolar aprotic solvent and/or acid;

b) mixing the dipolar aprotic solvent and/or acid in a pharmaceutically acceptable aqueous secondary solvent; and

c) removing the dipolar aprotic solvent and/or acid,

whereby the dipolar aprotic solvent and/or acid is eliminated or virtually eliminated from the solvent vehicle.

84.(amended) The solvent vehicle of claim 26, wherein the process further comprises reconstituting the composition in a pharmaceutically acceptable aqueous solution.

85.(amended) The solvent vehicle of claim 84, wherein said pharmaceutically acceptable aqueous solution comprises water, saline solution, dextrose solution, aqueous lipid emulsion, glacial acetic acid, or lipid solution.

86.(amended) The solvent vehicle of claim 84, wherein said pharmaceutically acceptable aqueous solution comprises water.

87.(amended) The solvent vehicle of claim 84, wherein said pharmaceutically acceptable aqueous solution comprises saline solution.

88.(amended) The solvent vehicle of claim 84, wherein said pharmaceutically acceptable aqueous solution comprises dextrose solution.

89.(amended) The solvent vehicle of claim 88, wherein said dextrose solution comprises 5% to 70% dextrose in water.

90.(amended) The solvent vehicle of claim 88, wherein said dextrose solution comprises 5% or 10% dextrose solution.

91.(amended) The solvent vehicle of claim 84, wherein said secondary solvent comprises a parenteral infusion fluid.

93.(amended) A method for preparing a pharmaceutically acceptable solvent vehicle comprising:

a) obtaining a pharmaceutically acceptable dipolar aprotic solvent and/or acid;

b) mixing the dipolar aprotic solvent and/or acid in a pharmaceutically acceptable aqueous secondary solvent; and

c) removing the dipolar aprotic solvent and/or acid,

whereby the dipolar aprotic solvent or acid is eliminated or virtually eliminated from the solvent vehicle.

94.(amended) The method of claim 93, where the acid is acetic acid.

95.(amended) The method of claim 93, where the dipolar aprotic solvent and/or acid is virtually eliminated from the solvent vehicle.

96.(amended) The method of claim 93, where removing the dipolar aprotic solvent and/or acid is by lyophilization.

97.(amended) The method of claim 93, further comprising reconstituting the composition by the addition of a pharmaceutically acceptable aqueous solvent.

98.(amended) The method of claim 97, wherein said pharmaceutically acceptable aqueous solution comprises water, saline solution, dextrose solution, aqueous lipid emulsion, glacial acetic acid, or lipid solution.

99.(amended) The method of claim 93, further comprising the step of dissolving pimaricin in said dipolar aprotic solvent and/or acid prior to mixing in a pharmaceutically acceptable aqueous secondary solvent.

100.(new) The solvent vehicle of claim 26, further comprising the step of dissolving pimaricin in said dipolar aprotic solvent and/or acid prior to mixing in a pharmaceutically acceptable aqueous secondary solvent.

101.(new) A pharmaceutically acceptable solvent vehicle, capable of solubilizing a drug, prepared by a process comprising;

a) mixing a drug in a pharmaceutically acceptable dipolar aprotic solvent and/or acid;

b) further mixing the composition of step a) in a pharmaceutically acceptable aqueous secondary solvent; and

c) removing the dipolar aprotic solvent and/or acid,

whereby the dipolar aprotic solvent or acid is eliminated or virtually eliminated from the solvent vehicle.

102.(new) The solvent vehicle of claim 101, wherein the drug is pimaricin.

103.(new) The solvent vehicle of claim 26, wherein the dipolar aprotic solvent or acid is eliminated.

104.(new) The solvent vehicle of claim 26, wherein the removing dipolar aprotic solvent or acid removes 95% of the dipolar aprotic solvent or acid.

105.(new) The solvent vehicle of claim 104, wherein the removing dipolar aprotic solvent or acid removes 99% of the dipolar aprotic solvent or acid.

106.(new) The method of claim 93, wherein the dipolar aprotic solvent or acid is eliminated.

107.(new) The method of claim 93, wherein the removing dipolar aprotic solvent or acid removes 95% of the dipolar aprotic solvent or acid.

108.(new) The method of claim 107, wherein the removing dipolar aprotic solvent or acid removes 99% of the dipolar aprotic solvent or acid.

II. RESPONSE TO OFFICE ACTION

A. Status of Claims

Claims 26, 84, 85, 86, 87, 88, 89, 90, 91, 93, 94, 95, 96, 97, 98 and 99 have been amended. New claims 100, 101, 102, 103, 104, 105, 106, 107, and 108 have been added. Thus,

claims 26-48, 50-68, 81-108 are presently pending in this case. Attached hereto as **Appendix A** is marked-up copy of the amended claim. A clean copy of all pending claims is also attached hereto as **Appendix B** for the convenience of the Examiner.

B. Support for the Claims

Specifically, support for claim 26, which describes solvent vehicles of the invention can be found in the specification at least on page 5, lines 8-30, page 10, lines 6-8, page 10, lines 25-30, page 11, lines 1-6 and page 14, lines 25-29.

Additional evidence for the support of the terms "eliminating" or "virtually eliminating" in claim 26 is also presented in the form of a inventor declaration under 37 C.F.R. §1.132 by Dr. Borje S. Andersson, submitted herewith as **Exhibit A**. The declaration by Dr. Andersson provides data obtained by gas-chromatography/mass-spectroscopy (GC/MS) analysis of the instant solvent vehicles which is an assay used routinely in the art to analyze the presence of residual organic solvents. As described in Exhibit A, GC/MS analysis of samples of solvent vehicle, exemplified by N'N-dimethlyacetamide (DMA) as a dipolar aprotic solvent and Intralipid™ (an aqueous lipid emulsion) as a secondary aqueous solvent, showed that the DMA content was "virtually eliminated" in 3 out of six cases (with only 1.7%., 1.1% and 1.0% being detected in these samples) and "eliminated" in the other 3 samples where no detectable DMA was seen. Thus, 98% or more of the dipolar aprotic solvent or acid was shown to be eliminated by these methods.

Claim 84 has been amended to clarify that it is the solvent vehicle of claim 26 that can be further reconstituted in a pharmaceutically acceptable aqueous solvent. This amendment is to

overcome a 35 U.S.C. §112, second paragraph, rejection of indefiniteness raised in the pending Action to claim 84. Support for claim 84 is found in the specification at least on page 5, lines 8-21 and pages 22 and 23.

Claims 85, 86, 87, 88, 89, 90, 91, 94, 95, 96, 97, 98 and 99 have been amended to correct their dependencies.

Support for claims 93 which describes methods of making the solvent vehicles can be found in the specification at least at on page 5, lines 8-30, page 10, lines 6-8, page 10, lines 25-30, page 11, lines 1-6 and page 14, lines 25-29.

Claim 97 has been amended to clarify the composition of the solvent vehicle in a fashion similar to claim 84.

Claim 99 and claim 100 describe the step of mixing pimaricin with the dipolar aprotic solvent or acid prior to mixing with a secondary aqueous solvent. Support for claims 99, 100, 101 and 102 and can be found in the specification at least at on page 5, lines 8-30, page 10, lines 6-8, page 10, lines 25-30 and page 11, lines 1-6.

Claim 103 is dependent on claim 26 and recites that the dipolar aprotic solvent or acid can be "eliminated" from the solvent vehicle. Claims 104 and 105 describe the percentage of dipolar aprotic solvent or acid that may be removed from the solvent vehicle and are supported at least on page 5, lines 14-15 of the specification. Claim 106 recites that the dipolar aprotic solvent or acid can be eliminated from the solvent vehicle and is dependent on claim 93. Claims 107 and 108 describe the percentage of dipolar aprotic solvent or acid that may be removed from the solvent vehicle prepared by the method of claim 93 and are supported at least on page5, lines 14-15 of the specification.

No new matter is added by these amendments.

C. Non-Elected Invention

The Examiner has withdrawn from consideration claims 16-23, 49, 68-80, 83 and 92-99 as being drawn to a non-elected invention.

While it is true that claims 16-23 and 69-80, belong to non-elected species, Applicants respectfully traverse the withdrawal of claims 68, 83 and 92-99 based on the previous Restriction Requirement in this case. In the Response to Restriction Requirement, Applicants had elected claims of Group II which are the claims directed to solvent vehicles. This group consists of claims 26-68 (see page 2 of Restriction Requirement, dated October 25, 2000), and new claims 81-99 that were added in the previous response to Office Action. In the present Action the Examiner has said that claim 68 is withdrawn. However, claim 68 is drawn to a solvent vehicle and is dependent on claim 26. The same is true for claims 83 and 92 which are also claims dependent on claim 26 and are claims that concern the solvent vehicle. Therefore, Applicants contend that claims 68, 83 and 92 are claims that are **not withdrawn** by the Restriction Requirement and Applicants do not see any reason to withdraw these claims from consideration.

Furthermore, the Examiner has also withdrawn claims 93-99 which are method claims directed to methods of making the solvent vehicle. In the current Office Action, the Examiner has **wrongly alleged** that the Applicants had submitted a request for continued examination (RCE) and cannot switch inventions and hence cannot claim methods for making solvent vehicles embodied by claims 93-99 (see page 2 of pending Office Action). On the contrary, Applicants had submitted a continued prosecution application (CPA) **and not an RCE**. Applicants have discussed this with the Examiner in several phone conferences and two Interview Summaries from the Examiner clarify that the Applicants had indeed submitted a CPA

and not a RCE. Although, the Examiner reissued the Office Action following the first phone interview, the reissued Action has several typographic errors and still refers to the CPA as an RCE in some instances. Especially, the section that describes the withdrawal of claims 93-99 alleging inability to switch invention in a RCE has not been revised. In the second Interview Summary the Examiner has acknowledged this error and therefore Applicants **do not** consider these claims as withdrawn.

In addition, the method claims 92-99 were filed in the CPA on December 21, 2001, by Applicants after discussions with the Examiner in which the Examiner had recommended that if a CPA was filed method claims for making the solvent vehicle would be examined. In subsequent phone conferences, Applicants were urged to remind the Examiner of these discussions in this Response.

Finally, as "solvent vehicles" were elected in the previous Response to Restriction Requirement these claims, *i.e.*, claims 68, 83 and 92-99, are not considered as withdrawn by Applicants as the subject matter of these claims is the elected "solvent vehicle". Hence, Applicants contend that claims 26-48, 50-68 and 81-99 are pending in the instant application. If Examiner has any reasons to the contrary, then an Action on Merits with the rejections addressing each of these claims will be required for it is the Examiner who retains the burden of explaining why these claims are rejected, if indeed they are rejected.

D. Rejection of Claims Under 35 U. S. C. § 112, First Paragraph

Drug Maybe Comprised in Solvent Vehicle

The Action has rejected claims 26-48, 50-67, 81, 82 and 84-91 under 35 U.S.C. §112, first paragraph, as containing subject matter not described in the specification to reasonably

convey to one skilled in the art that the inventors had possession of the invention at the time the application was filed. The Examiner alleges that as the amended claims comprise a drug along with the vehicle there is no separation of drug from vehicle. The Examiner has further alleged that the process of providing the vehicle does not exclude the drug and hence concludes that the claim to a vehicle is beyond the scope of the specification.

Applicants respectfully traverse. There is no question, as detailed in previous responses, that the specification separately contemplates solvent vehicles to be employed as drug carriers. Claim 26 describes that the solvent vehicles of the invention are prepared by obtaining a dipolar aprotic solvent and/or acid and mixing this in a secondary aqueous solvent followed by removing the dipolar aprotic solvent or acid thereby eliminating or virtually eliminating the dipolar aprotic solvent or acid from the solvent vehicles. Applicants however contend that the solvent vehicles of the invention can be made with a drug where the drug is dissolved in the dipolar aprotic solvent or acid prior to dissolving it in the secondary aqueous solvent and removing the dipolar aprotic solvent or acid.

As noted in the previous responses in this case (see the Preliminary Amendment dated October 8, 1999, on the section abridging pages 9 and 10), the specification describes these solvent vehicles and teaches methods for making such solvent vehicles. Thus, Applicants present that the specification is enabling for what is claimed and request withdrawal of the rejections raised.

Process of Preparing Vehicle

On page 4, first paragraph, of the Action the Examiner alleges that "no weight is given to the process of preparing the vehicle, as the vehicle preparation, absent drug, has not been shown

by applicant to provide any critical or different properties as a function of preparation, over prior art vehicles."

Applicants respectfully traverse. The discussion in the section above is incorporated here by reference. As discussed above, there is no question, that the specification separately contemplates solvent vehicles to be employed as drug carriers and describes methods to prepare such solvent vehicles. Claim 93 describes methods for preparing the instant solvent vehicles.

In view of the Examiners comments about the "critical or different properties as a function of preparation, over prior art vehicles," Applicants would like to note that the present method for preparing the pharmaceutically acceptable solvent vehicle results in the "elimination" or "virtual elimination" of the dipolar aprotic solvents or acid. This is supported by the specification and also by Exhibit A.

The instant specification describes that removal of virtually all of the organic component makes the vehicles extremely useful. For example, page 11, lines 2-5, describes how the removal of organic solvent, reduces the adverse effects related to organic solvents, such as hepatic side effects, maximizing patient safety after drug administration. In other examples, page 19, lines 13-26, describes the increased stability and longer shelf life following removal of organic solvents such as DMSO; page 20, lines 10-13, teach how to make isosmotic vehicles by reconstitution following lyophilization to remove organic solvents; and page 21, lines 6-9, describes other beneficial effects such as lowering of hemolytic potential of lyophilized formulations in which organic solvents are removed. Thus, the methods of the invention provide novel solvents that are virtually to completely free of residual organic solvents that are the cause of several side-effects.

In view of the above, Applicants request the withdrawal of this rejection to the method claims.

E. Rejection of Claims Under 35 U. S. C. § 112, Second Paragraph

Claims 82 and 84-91 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite in the Action.

The Term "Virtually"

Examiner has rejected claim 82 alleging that the term 'virtually' includes as much as 50% which is contrary to its normal usage and has required that the Applicants identify how much of the organic solvent is eliminated and how much remains.

Applicants respectfully traverse. Applicants have described in the Preliminary Amendment submitted with the filing of the CPA that the term 'virtually' is defined in the dictionary as 'almost entirely' and is intended to mean that the pharmaceutically acceptable solvent vehicle is 'substantially free of organic solvent' and/or that 'the major fraction of the organic/aprotic solvent' is removed, with "**preferably more than 95% and most preferably more than 99%**" or more of the organic solvent removed from the final vehicle (see specification, page 5, lines 14-15). This is supported by the specification at least on page 11, lines 2-6 and lines 21-24, describes that lyophilization "virtually eliminates the organic solvent" of the vehicle, which minimizes side-effects (such as hepatic side-effects) related to the vehicle's organic component. In addition, page 19, lines 5-17, describe that removal of "the major fraction of the organic solvent", such as DMA, allows reconstitution into an aqueous solvent, such as double-distilled water, **to obtain a very stable formulation which retained all its**

pharmacological activity. Furthermore, page 32, lines 10-15, describe that the step of lyophilization "virtually eliminates the final-use-preparation's content of the organic solvent."

In further support of this, Applicants present evidence in the form of a declaration under 37 C.F.R. §1.132 by the inventor, Dr. Borje S. Andersson, submitted herewith as **Exhibit A**. As described above, the declaration by Dr. Andersson provides data obtained by gas-chromatography/mass-spectroscopy (GC/MS) analysis of the instant solvent vehicles which is an assay used routinely in the art to analyze the presence of residual organic solvents. GC/MS analysis of samples of solvent vehicle, exemplified by N'N-dimethlyacetamide (DMA) as a dipolar aprotic solvent and Intralipid™ as a secondary aqueous solvent, that was lyophilized for 36 hours, showed that the DMA content was "virtually eliminated" in 3 out of six cases (with only 1.7%., 1.1% and 1.0% being detected in these samples) and "eliminated" in the other 3 samples where no detectable DMA was seen. Thus, 98% or more of the dipolar aprotic solvent or acid is eliminated by these methods by 36 hours of lyophilization.

One of skill in the art will appreciate that in order to make a pharmaceutically acceptable solvent vehicle all of the dipolar aprotic solvent or acid can be removed as shown in Exhibit A if required. However, removal of all the dipolar aprotic solvent or acid may not be necessary in some cases. For the purpose of making a "pharmaceutically acceptable vehicle" removal of dipolar aprotic solvents or acids to an acceptable amount may be required by a health regulating body. For example, the Food and Drug Administration (FDA) in its "Guidelines on Impurities: Residual Solvents," as published in the Federal Register, Volume 62., No. 247, December 24, 1997, pages 67377-67388, a copy of which is submitted herewith as **Exhibit F**, provides that the "permitted daily exposure" (PDE) to DMA is 10.9 mg/day in a 50 kilogram patient. The skilled

artisan will also appreciate that in the solvent vehicles described in Exhibit A where "virtual elimination" of DMA was achieved with 1.7%, 1.1% or 1.0% DMA being retained, merely extending the lyophilization time can further remove the dipolar aprotic solution or acid from the vehicle to bring it to the acceptable levels.

In view of this evidence, Applicants contend that the pharmaceutically acceptable solvent vehicles of the instant invention provide "elimination" or "virtual elimination" of the dipolar aprotic solvent or acid component thereby minimizing the side effects from contaminant organic solvent.

Lack of Clarity

The Examiner has also rejected claim 84, and its dependent claims 85 to 91, as lacking clarity. Applicants have amended claim 84 to clarify that it is the composition of claim 26 that can further be reconstituted in a pharmaceutically acceptable parenteral solvent. Claims 85-91 have also been amended to correct their dependency. As described in the section above all these amended claims are supported by the specification and the amendments do not introduce any new matter. Therefore, Applicants contend that the 35 U.S.C. § 112, indefiniteness issues have been resolved and request withdrawal of these rejections.

F. Rejection of Claims 26-28, 30-34, 41-45, 47, 48, 50-59, 63-67, 81, 82 and 84-91 Under 35 U.S.C. § 102(e) in View of U.S. Patents 5,559,148 or 5,430,057

Claims 26-28, 30-34, 41-45, 47, 48, 50-59, 63-67, 81, 82 and 84-91 have been rejected under 35 U.S.C. §102(e) as being anticipated by Andersson in U.S. Patents 5,559,148 (also referred to as '148) or 5,430,057 (also referred to as '057).

Applicants respectfully traverse the anticipation rejections made on basis of the '148 and the '057 patents. The Examiner has not identified any teaching or suggestion in the cited art regarding the "elimination" or "virtual elimination" of organic solvent (dipolar aprotic solvent or acid) from solvent vehicles.

In view of this, Applicants request withdrawal of these rejections.

G. Rejection of Claims 26, 27, 29, 32, 34-35, 37-42, 47, 48, 63-67, 81, 82 and 84-91 Under 35 U.S.C. § 102(e) in View of U.S. Patent 5,651,991

Claims 26, 27, 29, 32, 34-35, 37-42, 47, 48, 63-67, 81, 82 and 84-91 have been rejected 35 U.S.C. §102(e) as being anticipated by Sugiyama in U.S. Patent 5,651,991 (also referred to as the '991 patent).

Applicants respectfully traverse. The '991 patent describes drug carriers that comprise a fatty emulsion. For example, in column 5, lines 33-40, the '991 patent states that:

> "....the invention is characterized as follows: the drug carrier is a fat or fatty emulsion constituted by both a lipophilic substance as the core and a lipophilic substance as the surface layer...."

In contrast, the present invention claims pharmaceutically acceptable solvent vehicles that are made by obtaining a pharmaceutically acceptable dipolar aprotic solvent or acid and mixing with a pharmaceutically acceptable aqueous secondary solvent and then removing the dipolar aprotic solvent or acid to make a vehicle where the dipolar aprotic solvent or acid is eliminated or virtually eliminated.

In summary, the '991 patent **does not**: 1) describe dissolving drugs in dipolar aprotic solvents; and 2) does not describe the absence or removal of organic solvents from the final

composition. Thus, the vehicles of the present invention are clearly distinct and novel over the cited art. In view of this, the Examiner is requested to withdraw the 35 U.S.C. § 102 rejections based on '991.

H. Rejection of Claims 26-28, 30, 34, 36, 41, 47, 48, 52, 63-67, 81, 82 and 84-91 Under 35 U.S.C. § 102(b) as Anticipated by U.S. Patent 5,277,914 to Szoka *et al.*

Claims 26-28, 30, 34, 36, 41, 47, 48, 52, 63-67, 81, 82 and 84-91 are rejected under 35 U.S.C. 102(b) as being anticipated by Szoka *et al.*, 5,277,914 (also referred to as the '914 patent).

Applicants respectfully traverse. Applicants see no teachings, in columns 3, 4, 5, or 12 of the '914 patent that are cited by the Examiner, that describe the importance of "eliminating" or "virtually eliminating" the dipolar aprotic solvent or acid. Furthermore, the '914 patent does not even suggest reconstitution after removal of solvent in a pharmaceutically acceptable solvent as taught by the claims of the present application (see claim 84 of the instant application).

In view of this, Applicants request withdrawal of the rejections based on the '914 patent.

I. Rejection of Claims 26, 30, 34, 42, 63-65, 67, 81, 82 and 84-91 Under 35 U.S.C. § 102(b) as Being Anticipated by Pallado *et al.*, in WO 96/29998

Claims 26, 30, 34, 42, 63-65, 67, 81, 82 and 84-91 are rejected under 35 U.S.C. 102(b) as being anticipated by Pallado *et al.*, WO 96/29998. The Examiner has alleged that Pallado *et al.*, teaches that the process of making the MS involves dissolving the polysaccharide in an aprotic solvent and removal of aprotic solvent from the final composition.

Applicants respectfully traverse. The Examiner has failed to identify that the Pallado *et al.* application teaches an element of the present claims which is "mixing the dipolar aprotic

solvent (or drug and dipolar aprotic solvent) with a pharmaceutically acceptable secondary solvent" which is then followed by removal of the dipolar aprotic solvent.

As the Pallado *et al.* application does not teach an important feature of the present invention Applicants request the withdrawal of the anticipation rejections raised.

J. Rejection of Claims 26-28, 50-67, 81, 82 and 84-91 Under 35 U.S.C. §103(a) as Being Obvious over U.S. Patent 5,430,057 in View of U.S. Patent 5,651,991.

The Examiner has also presented an obviousness rejection to claims 26-28, 50-67, 81, 82 and 84-91 under 35 U.S.C. § 103(a) as being unpatentable over the 5,430,057 patent to Andersson *et al.*, in view of the 5,651,991 patent to Sugiyama.

Applicants respectfully traverse. As set forth above, the pharmaceutically acceptable solvent vehicles of the present invention are distinguished in that the dipolar aprotic solvent or acid is "eliminated" or "virtually eliminated."

The discussion of the '057 and '991 patents in the section above regarding the 35 U.S.C. § 102 rejections is incorporated herein by reference. Briefly, the Examiner has failed to identify if the '057 patent teaches the "elimination" or "virtually elimination" of dipolar aprotic solvents or acids. The '991 patent does not describe 1) mixing drugs in dipolar aprotic solvents; and 2) does not describe the absence or removal of organic solvents from the final composition. Neither of these references, individually or in combination, teach the removal of organic component.

Thus, even if one combines the teachings of '991 and '057 one would not reach at the instant pharmaceutically acceptable solvent vehicles as neither of these patents describe the need to remove **or** the removal of organic components from the final compositions. Thus, Applicants present that the obviousness rejection is moot and request withdrawal of this rejection.

III. CONCLUSION

In light of the above, the Examiner is requested to reconsider the pending rejections. It is submitted that the present response is a complete response, and that the claims are now in condition for allowance. If the Examiner has any questions or comments, he is earnestly requested to contact the undersigned representative.

Respectfully submitted,

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Date: September 18, 2002

APPENDIX A

MARKED-UP VERSION OF AMENDED CLAIMS

26.(amended) A pharmaceutically acceptable solvent vehicle[, capable of solubilizing a drug with low aqueous solubility,] prepared by a process comprising;

a) [dissolving a drug with low aqueous solubility in] obtaining a pharmaceutically acceptable dipolar aprotic solvent and/or acid;

b) [further dissolving] mixing the [composition of step a)] dipolar aprotic solvent and/or acid in a pharmaceutically acceptable aqueous secondary solvent; and

c) removing the dipolar aprotic solvent and/or acid [from the composition of step b).] ,

whereby the dipolar aprotic solvent and/or acid is eliminated or virtually eliminated from the solvent vehicle.

84.(amended) The solvent vehicle of claim 26, wherein the process further comprises reconstituting the composition [of step c)] in a pharmaceutically acceptable aqueous solution.

85.(amended) The solvent vehicle of claim [72] 84, wherein said pharmaceutically acceptable aqueous solution comprises water, saline solution, dextrose solution, aqueous lipid emulsion, glacial acetic acid, or lipid solution.

86.(amended) The solvent vehicle of claim [73] 85, wherein said pharmaceutically acceptable aqueous solution comprises water.

87.(amended) The solvent vehicle of claim [73] 85, wherein said pharmaceutically acceptable aqueous solution comprises saline solution.

88.(amended) The solvent vehicle of claim [73] 85, wherein said pharmaceutically acceptable aqueous solution comprises dextrose solution.

89.(amended) The solvent vehicle of claim [76] 88, wherein said dextrose solution comprises 5% to 70% dextrose in water.

90.(amended) The solvent vehicle of claim [76] 88, wherein said dextrose solution comprises 5% or 10% dextrose solution.

91.(amended) The solvent vehicle of claim [73] 84, wherein said secondary solvent comprises a parenteral infusion fluid.

93.(amended) A method for preparing a pharmaceutically acceptable solvent vehicle comprising:

a) obtaining a pharmaceutically acceptable dipolar aprotic solvent and/or acid;

b) [dissolving a drug with low aqueous solubility in said] mixing the dipolar aprotic solvent and/or acid;

[c) further dissolving composition of step b)] in a pharmaceutically acceptable aqueous secondary solvent; and

[d)] c) removing the dipolar aprotic solvent and/or acid, [from the composition of step c).]

whereby the dipolar aprotic solvent or acid is eliminated or virtually eliminated from the solvent vehicle.

94.(amended) The method of claim [81] 93, where the acid is acetic acid.

95. The method of claim [81] 93, where the dipolar aprotic solvent and/or acid is virtually eliminated from the solvent vehicle.

96.(amended) The method of claim [81] 93, where removing the dipolar aprotic solvent and/or acid is by lyophilization.

97.(amended) The method of claim [81] 93, further comprising reconstituting the composition [of step d)] by the addition of a pharmaceutically acceptable aqueous solvent.

98.(amended) The [solvent vehicle] method of claim [85] 97, wherein said pharmaceutically acceptable aqueous solution comprises water, saline solution, dextrose solution, aqueous lipid emulsion, glacial acetic acid, or lipid solution.

99.(amended) The method of claim [81] 93, [where the drug is pimaricin.] further comprising the step of dissolving pimaricin in said dipolar aprotic solvent and/or acid prior to mixing in a pharmaceutically acceptable aqueous secondary solvent.

-- 100.(new) The solvent vehicle of claim 26, further comprising the step of dissolving pimaricin in said dipolar aprotic solvent and/or acid prior to mixing in a pharmaceutically acceptable aqueous secondary solvent.

101.(new) A pharmaceutically acceptable solvent vehicle, capable of solubilizing a drug, prepared by a process comprising;

a) mixing a drug in a pharmaceutically acceptable dipolar aprotic solvent and/or acid;

b) further mixing the composition of step a) in a pharmaceutically acceptable aqueous secondary solvent; and

c) removing the dipolar aprotic solvent and/or acid,

whereby the dipolar aprotic solvent or acid is eliminated or virtually eliminated from the solvent vehicle.

102.(new) The solvent vehicle of claim 101, wherein the drug is pimaricin.

103.(new) The solvent vehicle of claim 26, wherein the dipolar aprotic solvent or acid is eliminated.

104.(new) The solvent vehicle of claim 26, wherein the removing dipolar aprotic solvent or acid removes 95% of the dipolar aprotic solvent or acid.

105.(new) The solvent vehicle of claim 104, wherein the removing dipolar aprotic solvent or acid removes 99% of the dipolar aprotic solvent or acid.

106.(new) The method of claim 93, wherein the dipolar aprotic solvent or acid is eliminated.

107.(new) The method of claim 93, wherein the removing dipolar aprotic solvent or acid removes 95% of the dipolar aprotic solvent or acid.

108.(new) The method of claim 107, wherein the removing dipolar aprotic solvent or acid removes 99% of the dipolar aprotic solvent or acid.--

APPENDIX B

CLEAN VERSION OF PENDING CLAIMS

26. A solvent vehicle prepared by a process comprising;

a) obtaining a pharmaceutically acceptable dipolar aprotic solvent and/or acid;

b) mixing the dipolar aprotic solvent and/or acid in a pharmaceutically acceptable aqueous secondary solvent; and

c) removing the dipolar aprotic solvent and/or acid,

whereby the dipolar aprotic solvent and/or acid is eliminated or virtually eliminated from the solvent vehicle.

27. The solvent vehicle of claim 26, wherein said aprotic solvent comprises N,N-dimethylacetamide, castor oil, dimethylsulfoxide, 1,2,-propylene-diol, glycerol or polyethylene glycol-400.

28. The solvent vehicle of claim 27, wherein said aprotic solvent comprises N,N-dimethylacetamide.

29. The solvent vehicle of claim 27, wherein said aprotic solvent comprises castor oil.

30. The solvent vehicle of claim 27, wherein said aprotic solvent comprises dimethylsulfoxide.

31. The solvent vehicle of claim 27, wherein said aprotic solvent comprises 1,2,-propylene-diol.

32. The solvent vehicle of claim 27, wherein said aprotic solvent comprises glycerol.

33. The solvent vehicle of claim 27, wherein said aprotic solvent comprises polyethylene glycol-400.

34. The composition of claim 26, wherein said secondary solvent comprises aqueous lipid emulsion, water, saline solution, dextrose solution, glacial acetic acid, or lipid solution.

35. The solvent vehicle of claim 34, wherein said secondary solvent comprises an aqueous lipid emulsion.

36. The solvent vehicle of claim 35, wherein said aqueous lipid emulsion comprises emulsified fat particles of about 0.4 micron in diameter.

37. The solvent vehicle of claim 35, wherein said aqueous lipid emulsion comprises an aqueous soy bean lipid emulsion.

38. The solvent vehicle of claim 37, wherein said aqueous soy bean lipid emulsion comprises soy bean oil, lecithin, glycerin and water.

39. The solvent vehicle of claim 35, wherein said aqueous lipid emulsion comprises a lipid component that includes at least one vegetable oil and at least one fatty acid.

40. The solvent vehicle of claim 39, wherein said lipid component comprises at least about 5% by weight soybean oil and at least about 50% by weight fatty acids.

41. The solvent vehicle of claim 34, wherein said secondary solvent comprises water.

42. The solvent vehicle of claim 34, wherein said secondary solvent comprises saline solution.

43. The solvent vehicle of claim 34, wherein said secondary solvent comprises dextrose solution.

44. The solvent vehicle of claim 43, wherein said dextrose solution comprises 5% to 70% dextrose in water.

45. The solvent vehicle of claim 44, wherein said dextrose solution comprises 5% or 10% dextrose solution.

46. The solvent vehicle of claim 34, wherein said secondary solvent comprises glacial acetic acid.

47. The solvent vehicle of claim 26, wherein said secondary solvent comprises a lipid solution.

48. The solvent vehicle of claim 26, wherein said secondary solvent comprises a parenteral infusion fluid.

50. The solvent vehicle of claim 26, wherein said solvent vehicle comprises anhydrous N,N-dimethylacetamide and polyethylene glycol-400.

51. The solvent vehicle of claim 26, wherein said solvent vehicle comprises glacial acetic acid and polyethylene glycol-400.

52. The solvent vehicle of claim 26, wherein said solvent vehicle comprises anhydrous N,N-dimethylacetamide and aqueous lipid.

53. The solvent vehicle of claim 52, wherein said aqueous lipid is an aqueous soy bean lipid emulsion comprising soy bean oil, lecithin, glycerin and water.

54. The solvent vehicle of claim 53, wherein said solvent vehicle comprises anhydrous N,N,-dimethylacetamide and an aqueous soy bean lipid emulsion comprising soy bean oil, lecithin, glycerin and water in a 1:10 volume ratio.

55. The solvent vehicle of claim 53, wherein said solvent vehicle comprises anhydrous N,N,-dimethylacetamide diluted with 9 volumes 20% of an aqueous soy bean lipid emulsion comprising soy bean oil, lecithin, glycerin and water.

56. The solvent vehicle of claim 53, wherein said solvent vehicle further comprises normal saline or 5% dextrose solution.

57. The solvent vehicle of claim 26, wherein said solvent vehicle comprises anhydrous N,N-dimethylacetamide, polyethylene glycol-400 and 1,2-propylene diol.

58. The solvent vehicle of claim 26, wherein said solvent vehicle comprises anhydrous N,N-dimethylacetamide, polyethylene glycol-400, 1,2-propylene diol and dimethylsulfoxide.

59. The solvent vehicle of claim 58, wherein said solvent vehicle comprises anhydrous N,N,-dimethylacetamide, polyethylene glycol-400, 1,2-propylene diol and dimethylsulfoxide in equal volume ratios.

60. The solvent vehicle of claim 26, wherein said vehicle comprises glacial acetic acid, and wherein said vehicle further comprises anhydrous N,N,-dimethylacetamide, dimethylsulfoxide or an aqueous soy bean lipid emulsion comprising soy bean oil, lecithin, glycerin and water.

61. The solvent vehicle of claim 26, wherein said solvent vehicle comprises glacial acetic acid, dimethylsulfoxide and an aqueous soy bean lipid emulsion comprising soy bean oil, lecithin, glycerin and water.

62. The solvent vehicle of claim 61, wherein said solvent vehicle comprises glacial acetic acid, dimethylsulfoxide, and an aqueous soy bean lipid emulsion comprising soy bean oil, lecithin, glycerin and water in a 2:6:3 volume ratio.

63. The solvent vehicle of claim 26, wherein said composition is administered to an animal.

64. The solvent vehicle of claim 26, wherein said composition is administered to a human.

65. The solvent vehicle of claim 26, wherein said composition is administered by parenteral injection.

66. The method of claim 65, wherein said parenteral injection is intravascular or intraveneous injection.

67. The solvent vehicle of claim 26, wherein said composition is administered as an aerosol.

68. The solvent vehicle of claim 26, wherein said vehicle is lyophilized.

81. The solvent vehicle of claim 26, where the acid is acetic acid.

82. The solvent vehicle of claim 26, where the dipolar aprotic solvent and/or acid is virtually eliminated from the solvent vehicle.

83. The solvent vehicle of claim 26, where removing the dipolar aprotic solvent and/or acid comprises lyophilization.

84. The solvent vehicle of claim 26, wherein the process further comprises reconstituting the composition in a pharmaceutically acceptable aqueous solution.

85. The solvent vehicle of claim 84, wherein said pharmaceutically acceptable aqueous solution comprises water, saline solution, dextrose solution, aqueous lipid emulsion, glacial acetic acid, or lipid solution.

86. The solvent vehicle of claim 84, wherein said pharmaceutically acceptable aqueous solution comprises water.

87. The solvent vehicle of claim 84, wherein said pharmaceutically acceptable aqueous solution comprises saline solution.

88. The solvent vehicle of claim 84, wherein said pharmaceutically acceptable aqueous solution comprises dextrose solution.

89. The solvent vehicle of claim 88, wherein said dextrose solution comprises 5% to 70% dextrose in water.

90. The solvent vehicle of claim 88, wherein said dextrose solution comprises 5% or 10% dextrose solution.

91. The solvent vehicle of claim 84, wherein said secondary solvent comprises a parenteral infusion fluid.

92. The solvent vehicle of claim 26, wherein the drug with low aqueous solubility is pimaricin.

93. A method for preparing a solvent vehicle comprising:

a) obtaining a pharmaceutically acceptable dipolar aprotic solvent and/or acid;

b) mixing the dipolar aprotic solvent and/or acid in a pharmaceutically acceptable aqueous secondary solvent; and

c) removing the dipolar aprotic solvent and/or acid,

whereby the dipolar aprotic solvent and/or acid is eliminated or virtually eliminated from the solvent vehicle.

94. The method of claim 93, where the acid is acetic acid.

95. The method of claim 93, where the dipolar aprotic solvent and/or acid is virtually eliminated from the solvent vehicle.

96. The method of claim 93, where removing the dipolar aprotic solvent and/or acid is by lyophilization.

97. The method of claim 93, further comprising reconstituting the composition by the addition of a pharmaceutically acceptable aqueous solvent.

98. The method of claim 97, wherein said pharmaceutically acceptable aqueous solution comprises water, saline solution, dextrose solution, aqueous lipid emulsion, glacial acetic acid, or lipid solution.

99. The method of claim 93, further comprising the step of dissolving pimaricin in said dipolar aprotic solvent and/or acid prior to mixing in a pharmaceutically acceptable aqueous secondary solvent.

100. The solvent vehicle of claim 26, further comprising the step of dissolving pimaricin in said dipolar aprotic solvent and/or acid prior to mixing in a pharmaceutically acceptable aqueous secondary solvent.

101. A pharmaceutically acceptable solvent vehicle, capable of solubilizing a drug, prepared by a process comprising;

a) mixing a drug in a pharmaceutically acceptable dipolar aprotic solvent and/or acid;

b) further mixing the composition of step a) in a pharmaceutically acceptable aqueous secondary solvent; and

c) removing the dipolar aprotic solvent and/or acid,

whereby the dipolar aprotic solvent or acid is eliminated or virtually eliminated from the solvent vehicle.

102. The solvent vehicle of claim 101, wherein the drug is pimaricin.

103. The solvent vehicle of claim 26, wherein the dipolar aprotic solvent or acid is eliminated.

104. The solvent vehicle of claim 26, wherein the removing dipolar aprotic solvent or acid removes 95% of the dipolar aprotic solvent or acid.

105. The solvent vehicle of claim 104, wherein the removing dipolar aprotic solvent or acid removes 99% of the dipolar aprotic solvent or acid.

106. The method of claim 93, wherein the dipolar aprotic solvent or acid is eliminated.

107. The method of claim 93, wherein the removing dipolar aprotic solvent or acid removes 95% of the dipolar aprotic solvent or acid.

108. The method of claim 107, wherein the removing dipolar aprotic solvent or acid removes 99% of the dipolar aprotic solvent or acid.

LIST OF EXHIBITS

Exhibit A Declaration under 37 C.F.R. 1.132 by Borje S. Andersson

Exhibit B GC/MS Data

Exhibit C Mulligan *et al.*, 1995, *J. Chromatogr. Sci.* 33:49-54.

Exhibit D Camarasu *et al.*, 1998, *Pharm. Biomed. Anal.* 18:623-638

Exhibit E Li *et al.*, 2002, *Pharm. Biomed. Anal.*, 28, 673-682.

Exhibit F Federal Register, Volume 62. No. 247, December 24, 1997, pages 67377-67388.